Valley International Journals
Open Access Journal

International Journal of Medical Science and Clinical Inventions
Volume 2 issue 06 2015 page no. 981-993 ISSN: 2348-991X
Available Online At: http://valleyinternational.net/index.php/our-jou/ijmsci

Can Vitamin D Supplementation Help In The Treatment Of Metabolic Syndrome? An Experience at A Tertiary Level Hospital In Mumbai

Dr. Sangeetapednekar MBBS, MD[1] , Dr. Bhushandeore MBBS[2], Dr. Dharmendrapandey MBBS, MD[3], Dr. N.D. Moulick MBBS, MD[4]

[1]Professor, Department of Medicine, LokmanyaTilak Municipal Medical College and General Hospital, Sion, Mumbai. India.

[2]Postgraduate student, Department of Medicine, LokmanyaTilak Municipal Medical College and General Hospital, Sion, Mumbai. India.

[3]Assistant Professor, Department of Medicine, LokmanyaTilak Municipal Medical College and General Hospital, Sion, Mumbai. India.
Dr. N.D. Moulick MBBS, MD

[4]Head and Professor, Department of Medicine, LokmanyaTilak Municipal Medical College and General Hospital, Sion, Mumbai. India.

Corresponding author: Dr.SangeetaPednekar, MBBS, MD
Professor, Department of Medicine, LokmanyaTilak Municipal Medical College and General Hospital, Sion, Mumbai. India.
Email: drsangeeta27@gmail.com

ABSTRACT:
Introduction: Prevalence of metabolic syndrome (MS) range from 33 to 40% in India and obesity derived insulin resistance is considered to be the main culprit. Beneficial effect of vitamin D on insulin resistance has been shown previously. We aim to show the prevalence of vitamin D deficiency in patients who are diagnosed with insulin resistance and the effect vitamin D supplementation would have on various components of MS.
Methodology: All patients who presented to LokmanyaTilak Municipal Medical College and General Hospital, Mumbai from January 1, 2013 to December 31, 2013 were considered for the study. Patients who were diagnosed as MS according to the International Diabetes Federation criteria were consented and enrolled for the study. A set of biometric and biochemical investigations were done and were repeated after 10 weeks of vitamin D supplementation (60,000 IU sachet/week). Chi-square and t-test were applied to look for test of significance.
Results: 51 patients were included in the study; 65% males, 51.7 years mean age, 80% patients vitamin D deficient. We observed statistically significant decrease in waist circumference, body mass index, systolic and diastolic blood pressures, serum triglyceride, fasting blood sugar, fasting insulin levels, insulin resistance and hemoglobin A1c. Additionally, patients with vitamin D deficiency (<20ng/dL) showed the greatest response;fasting blood sugar decreased significantly (p=0.0072).
Conclusion: We support the practice of obtaining plasma vitamin D levels in patients at risk of or diagnosed with MS. Vitamin D supplementation resulted in statistically significant improvement in various biometric and biochemical markers of MS.

INTRODUCTON

The World Health Organization (WHO) has aptly recognized obesity as a major public health problem. [1] Obesity induced insulin resistance is considered to be the major driver of the clustering of interrelated metabolic disturbances (e.g. dyslipidemia, hyperglycemia, elevated blood pressure, raised blood sugars), often referred to as metabolic syndrome, thereby leading to an increased cardiovascular risk.[2] The prevalence of metabolic syndrome is on a rise with some studies estimating it to as high as 25% in the developed world.[3] In India the prevalence ranges from 33% to 40%.[4] It is well known that metabolic syndrome paves the way for chronic diseases like diabetes and cerebrovascular diseases. Metabolic syndrome increases the risk of diabetes anywhere from 9 – 30 times over the healthy population.[5] Furthermore, other concerns associated with metabolic syndrome are fat accumulation in liver (fatty liver), resulting in inflammation and the potential for cirrhosis, renal damage manifesting in form of microalbuminuria, obstructive sleep apnea, polycystic ovary syndrome and increased risk of cognitive decline in the elderly.

Although insulin resistance is thought to be the unifying pathophysiological mechanism underlying the metabolic syndrome, there is uncertainty regarding the prevalence and severity of insulin resistance in every patient with metabolic syndrome.[6] Thus we intend to analyze the association of insulin resistance; as derived by homeostasis model assessment of insulin resistance (HOMA-IR); in patients with metabolic syndrome.

Experimental studies have suggested that vitamin D may exert its beneficial effects by stimulating the expression of insulin receptor to improve insulin responsiveness for glucose transport or by controlling calcium influx, which is essential for the insulin mediated intracellular process in insulin responsive tissues.[7] Moreover, data from National Health and Nutrition Examination Survey (NHANES) III documented an ethnicdifference in the association between 25-hydroxy-vitamin D [25(OH)D]and insulin resistance, with a stronger association in

Caucasians than in African Americans, who have much lower levels of 25(OH)D concentrations. Our population, with 25(OH)D levels similar to those of African Americans, 25(OH)D was also negatively associated with fasting insulin and HOMA-IR, and the associations were stronger among overweight and obese subjects. Obesity is known to be associated with decreased bioavailability of vitamin D, which is sequestered in body fat.[8] Ye Z et al. reported a significant interaction between 25(OH)D and body mass index (BMI) on the risk for a 10-year increase in HOMA-IR.[9]

In addition, the release of free fatty acids from adipose tissue can induce insulin resistance, whereas 1,25- di-hydroxy-vitamin D has been shown to counteract the free fatty acid–induced insulin resistance.[10],[11] The stronger association of vitamin D with insulin resistance among the overweight and obese participants suggests that adequate vitamin D status is more important for the prevention of insulin resistance and metabolic syndrome in these individuals.[12]

This study was aimed to study prevalence vitamin D deficiency in metabolic syndrome and to study effect of oral vitamin D supplementation on glycemic control. We also sort to study the effect of oral vitamin D supplementation in improvement in insulin resistance

METHODOLOGY

Study design

After obtaining Institutional Ethics Committee approval, all patients who presented to medical, endocrine and geriatric outpatient and inpatient wards of LokmanyaTilak Municipal Medical College (LTMMC) and General Hospital, Mumbai from January 1, 2013 to December 31, 2013 were considered for the study. Patients who satisfied our inclusion and exclusion criteria (described below) were consented and included in the study. Demographic and clinical data were collected at the time of enrolment. As per the protocol of the study, after initial enrolment a set of investigations were sent for all patients after which all patients were prescribed oral Vitamin D 60,000 international unit (IU) sachet once a week

for 10 weeks. Patients were followed up after 3 months and the investigations were repeated.

Study setting

Mumbai is the most populous city in India, with an estimated metropolitan area population of 20.7 million according 2011 census.[13] Greater Mumbai has a literacy rate of 94.7%, which is higher than the national average of 86.7%. Apart from Marathi, which is the native language, Hindi, Gujarati and English are spoken and understood well in this region. LTMMC, a 1400 plus bedded academic tertiary level hospital, is a major healthcare provider in Sion, Mumbai.

Patient population

Patients aged 18 years or above were consented for the study. Patients were diagnosed as metabolic syndrome according to the International Diabetes Federation (IDF) consensus definition (Table 1).We excluded patients who had liver/renal failure, were pregnant at the time of enrolment, had skeletal abnormalities related to vitamin D, who refused to give consent and who were on drugs which would interfere with blood vitamin D levels like calcipotriene, digoxin, estrogen, isoniazide, bile acid sequestrants and anti-seizure medications.

Data collection and analysis

At the time of enrolment patients' weight, waist circumference was measured to calculate BMI for all patients. Vitals including heart rate, respiratory rate and blood pressures were noted. Blood samples were sent to measure serum triglyceride, serum vitamin D3, fasting blood sugar, fasting insulin and hemoglobin A1c. Fasting serum insulin level was done at an ISO accredited laboratory. Samples were transferred to the laboratory within 30 minutes of collection. The plasma 25(OH)D concentration was assayed with a radioimmunoassay kit (DiaSorin, Stillwater, MN).Insulin resistance was calculated using Homeostatic Model Assessment- Insulin Resistance (HOMA-IR). For the above-mentioned variables mean values and standard deviation were calculated. We performed these investigations before and after putting patients on Vitamin D3 treatment. Median [interquartile range (IQR)], mean and standard deviations (SD) were calculated for every anthropometric and

quantitative biochemical parameter. Mean change in values of various blood levels and p value to determine the significance of difference was calculated. We also looked at clinical variables like ejection fraction, presence of pedal edema and left ventricular hypertension as seen on two-dimensional echocardiography. Similar to previous analysis, these variables were noted before and after treatment with vitamin D3. Chi square test was used to calculate p values as a test of significance. For every analysis p value≤0.05 from two-sided tests was considered statistically significant. All the raw data was entered in Microsoft excel sheets and analyzed in SPSS statistical software (SPSS Inc, Chicago, USA).

RESULTS

During the abovementioned time period 51 patients satisfied our inclusion criteria. Mean age was 51.71±6.79 years (range 36-69 years) and 65% of the patients were males. We observed a mean decrease of 3.47±3.13 kilograms (p<0.001) (Table 2). Similarly we saw statistically significant decrease in waist circumference, BMI, systolic and diastolic blood pressure, serum triglyceride, fasting blood sugar, fasting insulin levels, insulin resistance and hemoglobin A1c (Table 2). However statistically insignificant change in percentage of patients with respect to ejection fraction, presence of pedal edema and left ventricular hypertension before and after treatment was seen (Table 3). In vitamin D deficient cases, a statistically significant decrease in fasting blood sugar was noted. 41 patients who were deficient in vitamin D (<20 ng/dL) had fasting blood sugar level of 167.27±24.73 mg/dL before starting treatment with vitamin D (Table 4). After 10 weeks of vitamin D supplementation, only 20 patients were deficient in vitamin D, and had mean fasting blood sugar of 152.70±16.30 mg/dL; the difference of before and after treatment sugar levels being statistically significant (p=0.0072).

DISCUSSION

WHO attempted to standardize the criteria to define metabolic syndrome in 1988.[14] In 2001, the National Cholesterol Education Program (NCEP) introduced the concept of metabolic syndrome into its guidelines to reduce

cardiovascular risk and came up with Adult Treatment Panel (ATP) III criteria.[15] The ATP III guidelines were intended to be more user friendly and provided both clinicians and epidemiologists with simple measures that were applicable in both clinical and research settings. In 2005, the International Diabetes Federation (IDF) proposed their own definition of metabolic syndrome intended for global application in clinical practice and represents modifications to the WHO definition and ATP III criteria (Table 1). The IDF places more emphasis on abdominal obesity as the core feature of the syndrome as it is independently associated with each of the other metabolic syndrome factors including insulin resistance. The IDF took an additional step to develop ethnic specific values for waist circumference cut off.

Metabolic Syndrome with its co morbidities presents an ever-increasing disease burden especially in urban India. This study provides evidence regarding clinical/biochemical profile of the patients with metabolic syndrome and association of plasma vitamin D and insulin resistance with 4 components of metabolic syndrome (dyslipidemia, hypertension, diabetes and central obesity).Plandevall et al. used confirmatory factor analysis to conclude that there is a single underlying factor like obesity that influences the expression of the traits of metabolic syndrome.[16] Patients in our study who were both obese and vitamin D deficient when treated with oral Vitamin D for 10 weeks showed improvement in obesity. BMI of our patients improved significantly after treatment with vitamin D, which correlated well with the findings of Ye Z et al.9Menuet R et al showed that elevated triglyceride in patients with metabolic syndrome is associated with vitamin D deficiency.[17] Our study had similar findings as serum triglyceride levels fell by 71.47±41.20 mg/dL ($p<0.001$) after treatment with vitamin D (Table 2). 80% of the patients were deficient in vitamin D at the time of enrolment (Table 3). There are inconsistent data that correlate vitamin D status with glucose homeostasis. Obtaining vitamin D levels are indicated in those who fit the criteria of metabolic syndrome, and there are reports, which favor this practice.[18]

Study by Reilly et al. found the additional measure of insulin resistance in association with metabolic syndrome to significantly improve outcomes in such patients. [19] Recent study by Abbasi et al. also found a positive correlation of HOMA-IR with all the components of metabolic Syndrome.[20] Our findings are similar to this and we therefore recommend quantifying insulin resistance using HOMA-IR in patients with metabolic syndrome. Referring to Indian data, our study partially conforms to the findings of Maheria et al [21] with the exception of hypertension. In their study significant association was found between insulin and hypertension, which was independent of adiposity. However they studied insulin resistance over a spectrum of both obese and lean population and hence they concluded that insulin resistance is probably a stronger risk factor for hypertension in lean individuals. However all cases included in our study had central obesity (as per IDF definition of metabolic syndrome) and hence such association could not be deduced.

Association of plasma vitamin D levels was statistically significant with waist circumference, BMI, serum triglyceride, fasting blood glucose, fasting insulin levels and blood pressure. To the best of our knowledge, the only work done on this association till date is by Abbasi et al[20] who found association of plasma vitamin D with all the components of metabolic syndrome. Plasma vitamin D promises to be an expedient biomarker for metabolic syndrome and its components. Its importance is highlighted by the fact that it is easily available, one time test does not require fasting samples and the results are available within 15 minutes of centrifugation of the sample.

LIMITATIONS

Our study has various limitations. Patients were enrolled from a single urban tertiary level hospital, so the results of this study might not be generalization to other geographical locations. In view of the widely prevalent nature of metabolic syndrome across the globe, our sample size might not be adequate to reach a definitive conclusion. This is in part due to the rigorous

inclusion/exclusion criteria we used and also due to the high cost of investigations involved which led to patients backing out of the study. Moreover, patients were followed only for 3 months, while metabolic syndrome is a chronic disorder. Future studies should follow patients for longer periods. Lastly, hyperinsulinemic-euglycemic clamp technique is the gold standard for assessment of insulin resistance, which could not be used due to unfeasibility. However HOMA-IR is a well accepted alternative methods.

CONCLUSIONS

Our findings demonstrate a strong correlation of vitamin D deficiency with various components of metabolic syndrome. Statistically significant improvement in various biometric and biochemical parameters has been seen in our patients after treatment with vitamin D for 10 weeks. Plasma vitamin D can be extended to screening of relatively younger obese population who have not yet developed all the components of metabolic syndrome, but are at a significant risk for the subsequent cardiovascular morbidities as result of obesity.

REFERENCES

[1]World Heath Report. Reducing risks, Promoting Healthy Life. World Health Organisation: Geneva, 2002.

[2]Grundy SM. Pre-diabetes, metabolic syndrome, and cardiovascular risk.J Am CollCardiol. 2012:14;59(7):635-643.

[3] Ford ES, Giles WH, Dietz WH. Prevalence of the metabolic syndrome among US adults: findings from the third National Health and Nutrition Examination Survey. AMA. 2002:16;287(3):356-359.

[4]Deedwania PC, Gupta R, Sharma KK, Achari V, Gupta B, Maheshwari A, Gupta A. High prevalence of metabolic syndrome among urban subjects in India: a multisite study. Diabetes MetabSyndr. 2014;8(3):156-161.

[5]Verhagen SN, Wassink AM, van der Graaf Y, Gorter PM, Visseren FL; SMART Study Group. Insulin resistance increases the occurrence of new cardiovascular events in patients with manifest arterial disease without known diabetes. the SMART study. CardiovascDiabetol. 2011:21;10:100.

[6]Bonora E, Kiechl S, Willeit J, Oberhollenzer F, Egger G, Meigs JB, Bonadonna RC, Muggeo M. Insulin resistance as estimated by homeostasis model assessment predicts incident symptomatic cardiovascular disease in caucasian subjects from the general population: the Bruneck study. Diabetes Care. 2007;30(2):318-324.

[7]Seida JC, Mitri J, Colmers IN, Majumdar SR, Davidson MB, Edwards AL, Hanley DA, Pittas AG, Tjosvold L, Johnson JA. Clinical review: Effect of vitamin D3 supplementation on improving glucose homeostasis and preventing diabetes: a systematic review and meta-analysis. JClinEndocrinolMetab. 2014;99(10):3551-3560.

[8]Wortsman J1, Matsuoka LY, Chen TC, Lu Z, Holick MF. Decreased bioavailability of vitamin D in obesity.Am J ClinNutr. 2000;72(3):690-693.

[9]Ye Z, Sharp SJ, Burgess S, Scott RA, Imamura F; InterAct Consortium, Langenberg C, Wareham NJ, Forouhi NG. Association between circulating 25-hydroxyvitamin D and incident type 2 diabetes: a mendelianrandomisation study. Lancet Diabetes Endocrinol. 2015;3(1):35-42.

[10]Wranicz J, Szostak-Węgierek D. Health outcomes of vitamin D. Part II. Role in prevention of diseases.RoczPanstwZaklHig. 2014;65(4):273-279.

[11] Alvarez JA, Ashraf A. Role of vitamin d in insulin secretion and insulin sensitivity for glucose homeostasis. Int J Endocrinol. 2010;2010:351385.

[12]von Hurst PR1, Stonehouse W, Coad J. Vitamin D supplementation reduces insulin resistance in South Asian women living in New Zealand who are insulin resistant and vitamin D deficient - a randomised, placebo-controlled trial. Br J Nutr. 2010;103(4):549-555.

[13]India stats: Million plus cities in India as per Census 2011". Press Information Bureau, Mumbai (Press release). Press Information Bureau, Government of India. 31 October 2011.

[14] Grundy S, Brewer B, Cleeman, J, Smith S, LenfantC. Definition of metabolic syndrome: Report of the National Heart, Lung and Blood Institute/American Heart Association Conference on scientific issues related to definition. Circulation. 2004:09;433-438.

[15]Zimmet, P. and Alberti, G. The metabolic syndrome: Perhaps an etiologic mystery but far from a myth-Where does the International Diabetes Federation Stand? Medscape Diabetes and Endocrinology, 7(2).

[16]Plandevall, M., Singal, B., Williams, L., Brotons, C., Guyer, H., Sadurni, J., Falces, C.,Serrano-Rios, M., Gabriel, R., Shaw, J., Zimmet, P. and Haffner, S. A single factor underlies the metabolic syndrome. Diabetes Care.2006:29(1), 113-122.

[17]Menuet, R., Lavie, C. and Milani, R. Importance and management of dyslipidemia in the metabolic syndrome.The American Journal of the Medical Sciences.2005:330(6), 295-302.

[18]Baz-Hecht M, GoldfineAB.The impact of vitamin D deficiency on diabetes and cardiovascular risk.CurrOpinEndocrinol Diabetes Obes. 2010;17:113–119.

[19] Reilly M., Wolfe, M., Rhodes, R., Girman, C., Mehta, N. and Rader, D. Measures of insulin resistance add incremental value to the clinical diagnosis of metabolic syndrome in association with coronary atherosclerosis. Circulation. 2004:110(7), 803-809.

[20]Ali Abbasi, Eva Corpeleijn, DouwePostmus, Ron T. Gansevoort, Paul E. de Jong. Plasma Procalcitonin Is Associated with Obesity, Insulin Resistance, and the Metabolic Syndrome: J ClinEndocrinolMetab, September 2010, 95(9):E26–E31.

[21]Maheria P, Parchwani D, Upadhyay A, Sharma MK. Analysis of insulin resistance in various components of metabolic syndrome. Natl J of Med Res. 2011,1(2): 37-41.

Table 1: International Diabetes Federation consensus definition of metabolic syndrome

1. Evidence of central obesity* (Increased waist circumference with ethnicity) • Male>90cm, • Female>80cm
2. Evidence of any two of the following – • Raised triglycerides: > 150 mg/dL (1.7 mmol/L), or specific treatment for this lipid abnormality • Reduced HDL cholesterol: < 40 mg/dL (1.03 mmol/L) in males < 50 mg/dL (1.29 mmol/L) in females specific treatment for this lipid abnormality • Raised blood pressure: systolic BP > 130 or diastolic BP >85 mm Hg, or specific treatment of previously diagnosed hypertension. • Raised fasting plasma glucose: >100 mg/dL (5.6 mmol/L), or specific treatment of previously diagnosed type 2 diabetes

*if Body Mass Index is >30kg/m^2, central obesity can be assumed and waist circumference does not need to be measured.

Table 2: Comparing patient biometric and biochemical markers before and after treatment with vitamin D

Patient characteristics	***n***	**Mean ± SD#**	**Mean change**	**p value***
Weight (kg)				
before treatment	51	79.16 ± 9.79	-3.47 ± 3.13	<0.001
after treatment	51	75.69 ± 9.60		
Waist circumference (cm)				
before treatment	51	106.43 ± 7.60	-3.84 ± 1.90	<0.001
after treatment	51	102.59 ± 7.23		
Body Mass Index (kg/m^2)				
before treatment	51	32.69 ± 4.59	-1.70 ± 1.72	<0.001
after treatment	51	30.99 ± 4.71		

Systolic blood pressure (mm of Hg)				
before treatment	51	150.55 ± 13.13.43	-12.82 ± 10.12	<0.001
after treatment	51	137.73 ± 8.46		
Diastolic blood pressure (mm of Hg)				
before treatment	51	87.65 ± 6.97	-6.39 ± 7.77	<0.001
after treatment	51	81.25 ± 5.45		
Serum triglyceride level (mg/dL)				
before treatment	51	286.27 ± 42.99	-71.47 ± 41.20	<0.001
after treatment	51	214.80 ± 46.87		
Serum Vitamin D3 level (ng/dL)				
before treatment	51	13.66 ± 6.82	+9.99 ± 6.02	<0.001
after treatment	51	23.65 ± 7.30		
Fasting blood sugar level (mg/dL)				
before treatment	51	169.00 ± 28.85	-21.20 ± 19.26	<0.001
after treatment	51	147.80 ± 18.01		
Fasting insulin level (mIU/L)				
before treatment	51	19.51 ± 8.22	-4.62 ± 4.57	<0.001
after treatment	51	14.89 ± 6.30		
Insulin resistance**				
before treatment	51	7.96 ± 3.25	-2.59 ± 1.96	<0.001
after treatment	51	5.37 ± 2.19		
Hemoglobin A1c %				
before treatment	51	7.95 ± 0.60	-0.27 ± 0.24	<0.001
after treatment	51	7.68 ± 0.51		

#SD = standard deviation

*p values <0.05 are statistically significant

**Insulin resistance quantified by using Homeostatic Model Assessment- Insulin Resistance (HOMA-IR) formula.

Table 3: Comparing clinical variables before and after treatment with vitamin D

Clinical variable	**Before treatment *n* (%)**	**After treatment *n* (%)**	**Significance on chi square test**
Ejection fraction			
20-30%	1 (2%)	2 (4%)	Not significant
31-40%	3 (6%)	2 (4%)	
41-50%	12 (24%)	14 (28%)	
51%-60%	19 (37%)	21 (41%)	
≥ 60%	16 (31%)	12 (23%)	
Vitamin D3 levels (ng/dL)			

< 20	41 (80%)	20 (39%)	Significant
21-29	9 (18%)	20 (39%)	(p< 0.001)
30-100	1 (2%)	11 (22%)	
Pedal edema			
present	11 (22%)	0 (0%)	Not significant
absent	40 (78%)	51 (100%)	
Left ventricular hypertension on 2 dimensional echocardiography			
present	14 (28%)	13 (26%)	Not significant
absent	37 (72%)	38 (75%)	

Table 4: Association of vitamin D3 level and fasting blood sugar level before and after treatment with vitamin D

Vitamin D3 level (ng/dL)	**Mean fasting blood sugar before treatment**		**Mean fasting blood sugar after treatment**	
	n	Mean ± standard deviation (mg/dL)	***n***	Mean ± standard deviation (mg/dL)
Deficiency (< 20)	41	*167.27 ± 24.73	20	152.70 ± 16.30
Insufficient (21 – 29)	09	178.78 ± 44.55	20	144.64 ± 25.34
Sufficient (30 – 100)	01	152.00 ± 0.00	11	148.36 ± 26.06

*by student's t test; p=0.0072; statistically significant